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A novel approach to the analysis of substituent effects: Quantitative description of ionization energies and gas basicity of amines

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In this work, a new topological approach based on simple matrix algebra is introduced to explore substituent effects at the level of atomic additivity in the absence of significant resonance contributions. In the framework of the suggested method, all atoms are classified according to element and valence state. The sums of the inverse squared distances between the substituent atoms and the reaction centre of the molecule are used as operational parameters in the present method. The approach implies atomic level of consideration of inductive and steric effects and allows for quantification of substituent effects without the use of pre-established group substituent constants. The practical application of the model is illustrated by the quantitative interpretation of ionization energies and gas basicity of a broad range of amines. Further development of the elaborated approach is also discussed. © 1999 by Elsevier Science Inc.

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INTRODUCTION

The elucidation of relationships between structure and reactivity of compounds is one of the major challenges in modern chemistry. Mono- and multiparametric free energy relationships (LFERs) allow mathematical formalization of quantitative structure–activity relationships in the framework of Hammett–Taft-type equations. The variables used in such equations are usually group substituent constants. A wide range of substituent parameters, extensively used in modern QSAR for drug design and molecular modeling and for studies of reactivity, physicochemical properties, and bioactivity, have been presented in numerous comprehensive reviews and monographs.[1–8] A large number of inductive (field), steric, and resonance constants for hundreds of diverse functional groups have been determined. These constants form many of the most commonly used substituent scales for studies of substituent effects at the group additivity level.

Relationships based on discrete distance-dependent atomic contributions have been derived, e.g., the model of the frontier steric effect and the additive model of inductive effect, which allow accurate theoretical calculation of steric and inductive constants of substituents through electronegativities and radii of the constituent atoms and intramolecular distances. A relevant description of these approaches and aspects of their application can be found in Refs. 2, 3, 9, and 10.

In this work we have combined these models into a unified topological technique for quantification of substituent effects in terms of discrete distance-dependent atomic contributions.

RESULTS AND DISCUSSION

Within the framework of the models mentioned in the introduction we have proposed that the steric and inductive effects can be described as follows.

Steric constants

The model assumes the frontal character of steric interactions.[3] The basis for this model is simple mechanical screening of the reaction center by the substituent atoms:

$$R'_S = \sum_{i=1}^{n} \frac{R_i^2}{4r_i^2} \qquad (1)$$

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